

# Effects of Glucagon and Tolbutamide on Plasma Insulin Levels in Children with Ketoacidosis

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## SUMMARY

The concentration of immunoreactive insulin in plasma has been determined following administration of tolbutamide and glucagon in seven children with newly diagnosed diabetic ketoacidosis. The basal plasma insulin levels were low, notwithstanding concomitantly high blood glucose levels. The plasma insulin concentration was increased by glucagon but not tolbutamide stimulation. These data suggest that a different mechanism of insulin release is induced by tolbutamide and glucagon. *DIABETES* 17:133-35, March, 1968.

Immunoassay technics for the measurement of insulin in plasma have only recently been used in studies of diabetes mellitus in childhood. Some observations have revealed that the juvenile diabetes does not respond with an increase in plasma insulin concentration following tolbutamide administration.<sup>1,2</sup> The present report describes the effects of glucagon and tolbutamide on plasma insulin concentration in children with diabetes mellitus.

## MATERIALS AND METHODS

Seven children with newly diagnosed diabetes mellitus and mild to moderately severe ketoacidosis were studied. None of the children had received insulin therapy previously. The investigative studies were initiated immediately after confirmation of the diagnosis of diabetes mellitus and before treatment with insulin and intravenous fluid was started.

The patients were stimulated with both intravenous tolbutamide (25 mg./kg.) and intravenous glucagon (20  $\mu$ g./kg.) in sequence. Four children were given tolbutamide initially, followed in one hour by intra-

venous glucagon. Three children received glucagon as the first stimulus, followed in one hour by tolbutamide.

Heparinized specimens of venous blood were obtained from the antecubital vein. Whole blood glucose was determined by the glucose oxidase method<sup>3</sup> and CO<sub>2</sub> content by the Astrup technic.<sup>4</sup> The concentration of insulin in plasma was determined by the radioimmunoassay technic of Hales and Randle.<sup>5</sup>

## RESULTS

Table 1 lists the chemical status of the seven children at the time of admission. In addition the sequence of tolbutamide and glucagon administration is also indicated.

In table 2 and in figures 1 and 2 the mean concentrations of plasma insulin in the seven diabetic children, following tolbutamide and glucagon administration, are compared with the responses in normal children.

The basal concentration of plasma insulin is significantly lower in the diabetic patients. Tolbutamide administration resulted in no increase in the concentration of insulin in the diabetic children in contrast to the prompt increase in the normals. Glucagon administration induced a significant rise in plasma insulin in both the diabetic and normal children. The rise in the diabetic children was appreciably less than that of the normals, however. Examination of the individual insulin values revealed no evidence that the sequence of drug administration affected the insulin responses. No increase in insulin concentration resulted from tolbutamide administration in any of the patients, while glucagon administration stimulated a rise in plasma insulin in all seven children.

## DISCUSSION

Samols et al. demonstrated that glucagon stimulates the secretion of insulin *in vivo*<sup>6</sup> independent of its hyperglycemic effect. A direct stimulatory effect of glucagon on insulin release by the isolated pancreas has also been

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EFFECTS OF GLUCAGON AND TOLBUTAMIDE ON PLASMA INSULIN LEVELS

TABLE 1  
Admission status of diabetic patients

Case No.	Age	Study sequence	Blood glucose mg. per 100 ml.	Plasma CO <sub>2</sub> mEq./L.	Plasma IRI μU./ml.
1	21 mos.	T-G	420	11.3	7.5
2	4 yrs.	G-T	126	14	9
3	7 yrs.	T-G	215	12	6
4	5 yrs.	G-T	310	13	4
5	10 yrs.	T-G	327	8.7	7.5
6	8 yrs.	G-T	340	9	4.5
7	6.5 yrs.	T-G	295	10.1	8

TABLE 2

Plasma insulin (μU./ml.) response to intravenous tolbutamide and glucagon in normal and diabetic ketoacidotic children\*

	N	Minutes after tolbutamide administration**				
		0	5	20	30	60
Normal†	18	14.40±2.60	<u>109.6±24</u>	<u>33.60±5.9</u>	<u>34.6±15.5</u>	19.20±9.4
Diabetic ketoacidotic	7	7.92±1.94§	8.92±1.79§	6.00±1.05§	6.83±1.03§	7.13±0.94§
		Minutes after glucagon administration				
		0	2	10	30	60
Normal‡	16	13.70±3	<u>73.80±12</u>	<u>31.20±10.10</u>	16± 5.10	12.10±2.70
Diabetic ketoacidotic	7	7.84±1.25§	<u>18.57±2.13§</u>	<u>14.28±1.89§</u>	8.43±1.61§	7.78±1.64

\*The dosage of tolbutamide and glucagon was 25 mg./kg. and 20 μg./kg.

\*\*Underlined values are statistically greater than group basal values at p < 0.01.

†Age 7-11 yrs.

‡Age 4-9 yrs.

All values are mean + S.E.M.

§Diabetic values are statistically less than paired normals at p < 0.01.

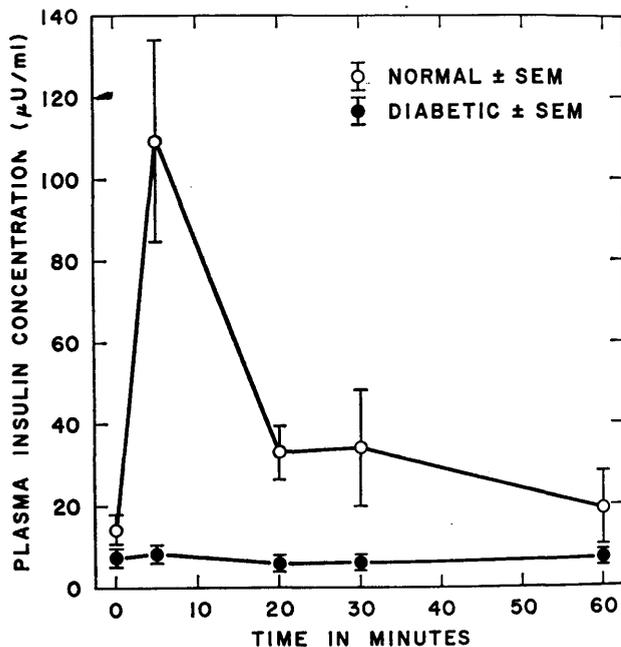


FIG. 1. Insulin responses of normal and diabetic children to tolbutamide administration.

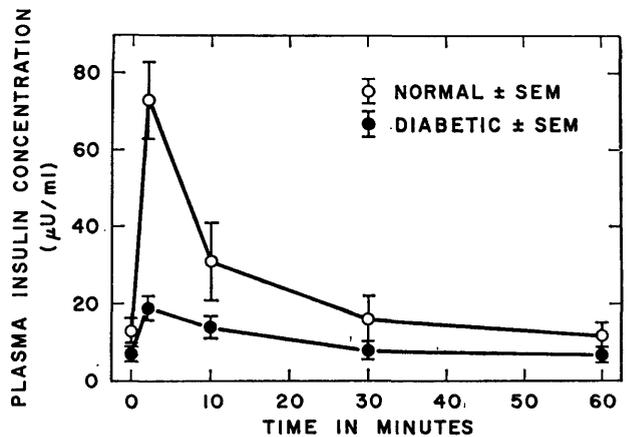


FIG. 2. Insulin responses of normal and diabetic children to glucagon administration.

demonstrated.<sup>7,8</sup> Recently, Simpson et al.<sup>9</sup> reported that when glucagon was injected intravenously with glucose, a rise in plasma insulin occurred in normal subjects and in noninsulin-dependent diabetic patients, while the injection of the same amount of glucose alone stimulated a significant rise in the concentration of plasma insulin only in the normal subjects. Thus, in some patients with mild diabetes mellitus, glucagon appears to augment the stimulatory effect of glucose, pharmacologically promoting a release of insulin which was not physiologically available after glucose.

Much indirect evidence suggests that tolbutamide stimulates insulin release by a mechanism different than glucose. The evidence for a unique beta-cytotropic effect of tolbutamide includes the effectiveness of the sulfonylurea compounds in the treatment of maturity onset diabetes mellitus, the induction of transitory leucine-sensitivity in normal subjects by pretreatment with tolbutamide<sup>10</sup> and obliteration of the diazoxide blockade of insulin-release by tolbutamide but not by hyperglycemia.<sup>11</sup>

The recent studies of Ryan et al.<sup>12</sup> of glucose, tolbutamide and glucagon stimulation of insulin release in the normal subject are compatible with the view that they would act by different mechanisms. The results of the present study could be interpreted in a similar fashion. Insulin deficiency in the presence of hyperglycemia and lack of an insulin response to tolbutamide administration might suggest complete islet-cell exhaustion at the time of study. But the release of insulin following glucagon administration conclusively demonstrates that the islets are not completely deficient of insulin and that this pharmacologic release mechanism remains functional, although somewhat less responsive than in normal.

Evidence that glucagon and tolbutamide stimulate

the beta cells by different mechanisms must be considered indirect, however. The observed differences may result from a greater dosage effect of glucagon. The problem might be resolved by similar studies employing a higher tolbutamide dose.

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